Behavior across levels of organization

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The major challenge in one word …

Integration

What are the integrative principles for the nervous system?

What are the organizational principles that integrate the myriad parts of the nervous system across many levels of organization and allow for the organism to behave as a unit?

What are the integrative strategies for neuroscience research?

How do we put together the fragmented knowledge about the pieces, and how do we coordinate fragmented research efforts to study the nervous system?

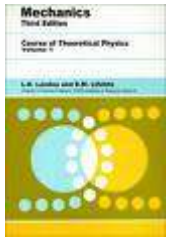
Two pieces to this talk:

- Theory as an integrative tool, and a branch of the theory that poses a challenge for further development.

- The levels of nervous system organization that need to be integrated to understand behavior, and a key challenge.

Theory as an integrative tool

- What would a comprehensive theoretical canon for biology look like?
- Cf: A Course in Theoretical Physics (Landau and Lifshitz …)



Mechanics

Elasticity

Fluids

EM

QM

Stat Phys

QED

Kinetics

Outlines of "A Course In Theoretical Biology"

- Biophysics, biochemistry (how questions) +
- A "theory of design", or engineering principles (why questions) +
- The theory of evolution (the bridge between the two)
- Knowledge management and systematic inference (informatics, statistics)

TOD: A research program

- Start with engineering theories (Three C's: Communication, Computation, Control)
- Apply the same principles across scales: intracellular networks, inter-cellular networks, physiology, societies/ecosystems
- Example: Homeostasis/feedback regulation
- Validation: Synthetic Biology (gain-of-function experimental manipulations)
- Integration with the Theory of Evolution

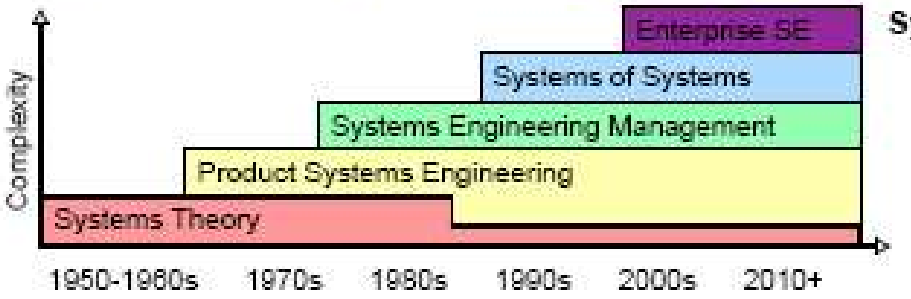
… a quote from Darwin …

".. when we contemplate every complex structure and instinct as the summing up of many contrivances, each useful to the possessor, nearly the same way as when we look at any great mechanical invention as the summing up of the labor, the experience, the reason, and even the blunders of numerous workmen; when we thus view each organic being, how much more interesting, I speak from experience, will the study of natural history become! "

Examples of integration across levels of organization, and a key challenge

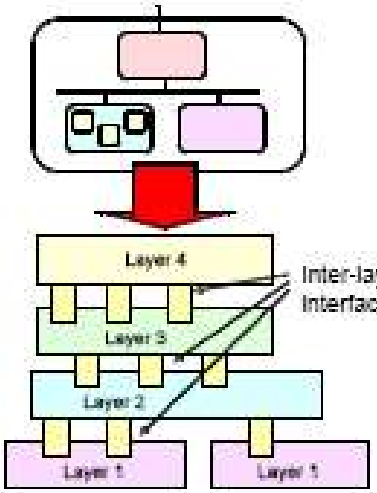
Modern engineering has evolved to integrate across levels of organization (Currently: "Enterprise Systems")

Systems of Systems Engineering (2004/2005 Studies)



Systems Engineering

- Process by which a customer's needs are satisfied
- Steps: conceptualization, design, modeling, testing, implementation, and operation of working system.



Systems of Systems Engineering

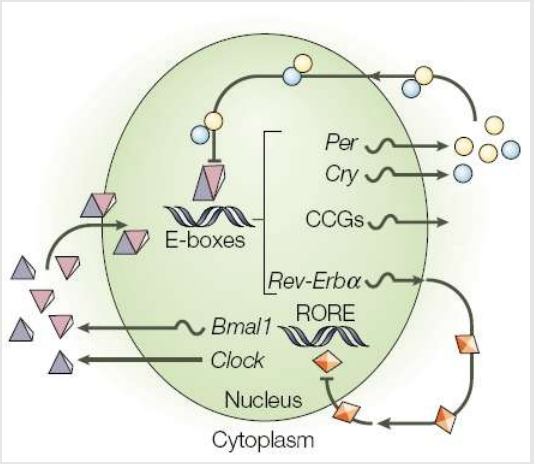
- Move from *single* (complex) system to a collectinon of systems that are designed for their own purposes
- Requires shift from hierarchies → *layers & interfaces*

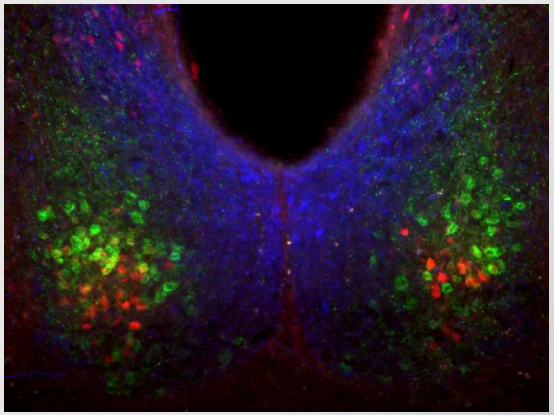
Research challenges

- How do we identify "convergent protocols" (fixed points) early in design phase?
- What metrics do we use to describe flexibility, evolvability, reconfigurability, robustness, etc

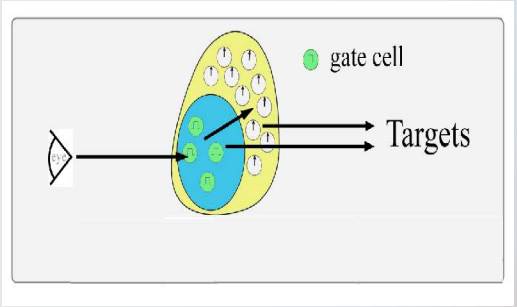
Integration example: Circadian Rhythms

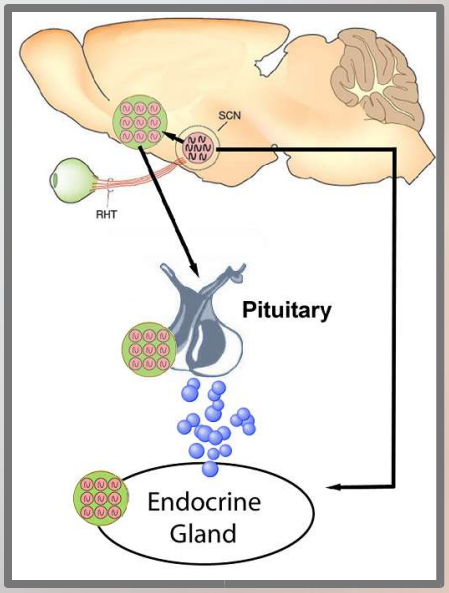
Molecular / Genetic



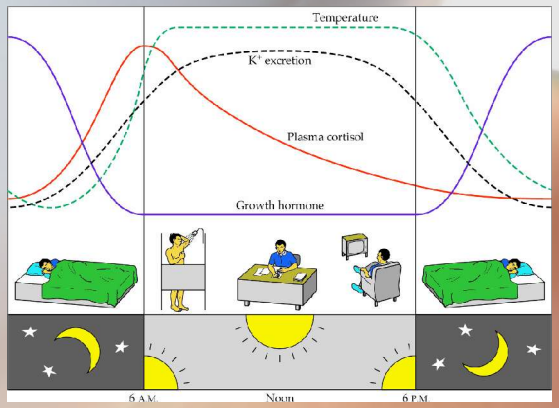


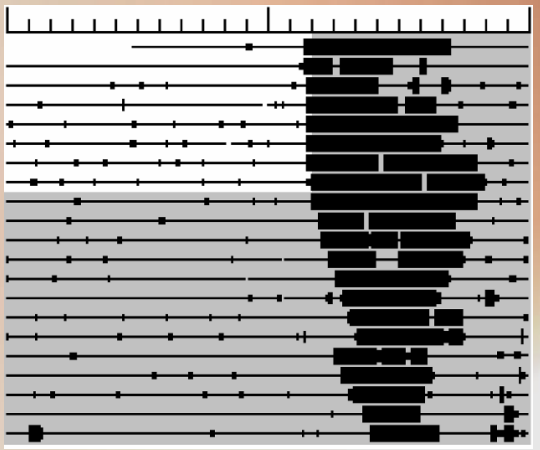
Neural/Organ Systems





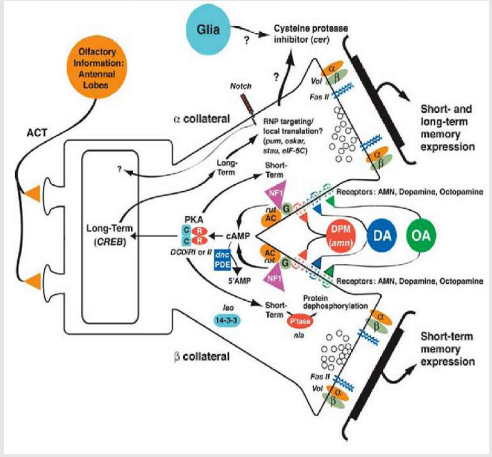
Behavior



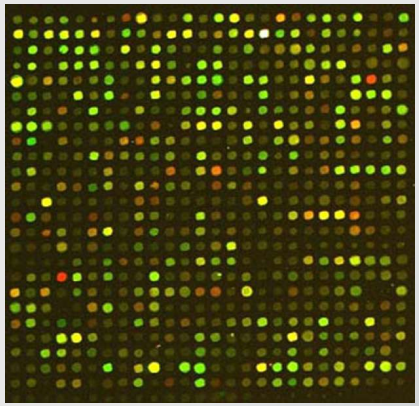


Integration challenge: Drosophila

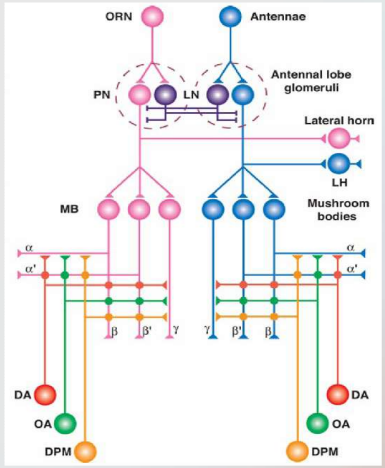
Molecular / Genetic



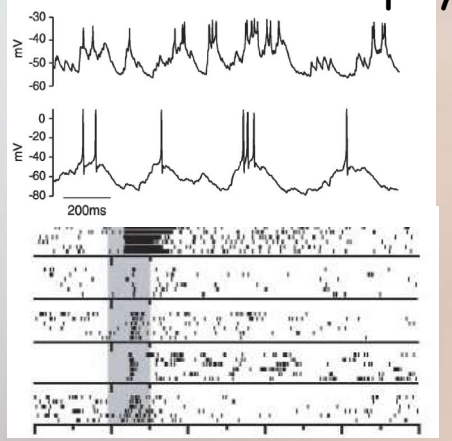
Got a good start here …



Neural

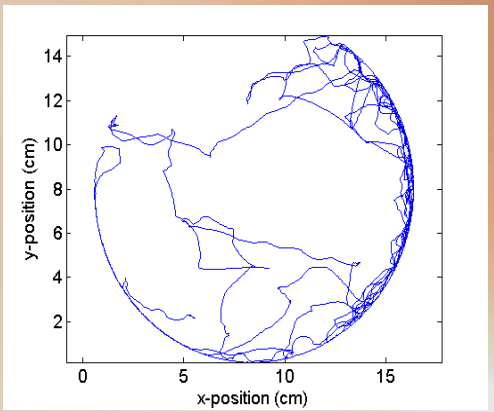


Need more electrophys



Behavior

Need detailed behavior



+ Need theory & informatics …

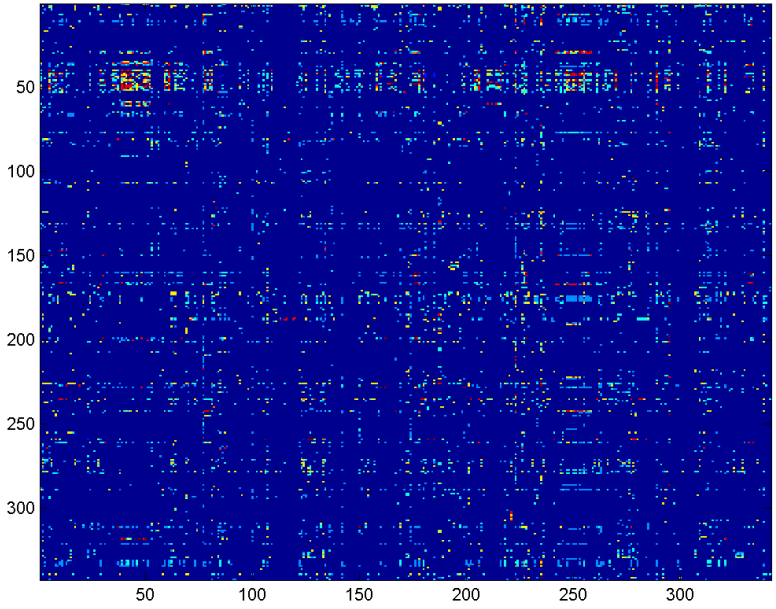
A critical missing piece: Need the Networks!

(meso-scale networks in particular ..
Experimental + Informatics Challenge! … cf: Genomes)

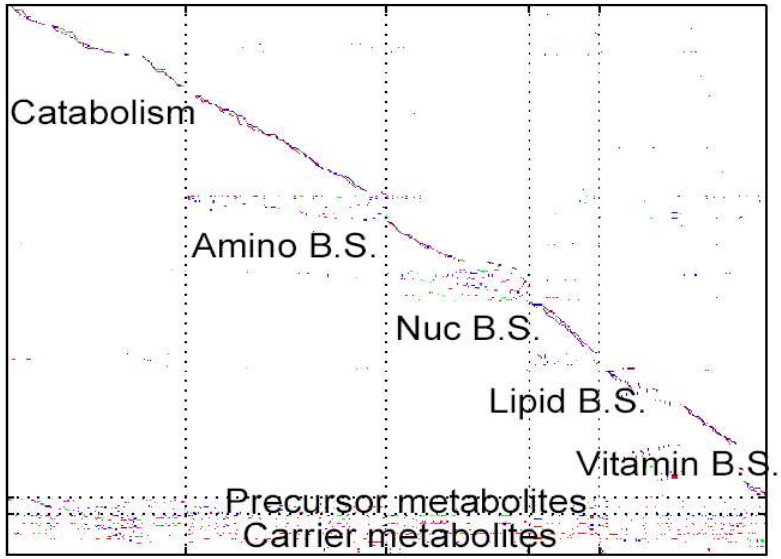
* Small circuits (in Lobster, Leech) √
* C Elegans √
* Drosophila
* Rat (BAMS, others)
* Macaque (Cocomac, others)
* Human !! (Some Beginnings:
  Brain Architecture project,
  Connectome project, etc)

Cellular networks are sometimes better characterized than (mesoscopic) brain networks …

Rodent brain connectivity from BAMS Connectivity matrix (Swanson,1998) (342 x 342). Blue=Unknown



Functional subsystems in bacterial metabolic network (Doyle)



Stoichiometry matrix for E Coli metabolism of 409 metabolites and 599 reactions arranged in functional modules

Summary

- Integration as key challenge: principles of nervous system integration; strategies for integrating research.
- A key theory challenge: TOD: engineering principles that apply across levels of organization.
- A key experimental and informatics challenge: Assemble the connectivity matrices, particularly the human brain. Cf: Genome project.